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SUPPLEMENTARY STATEMENTS*

A. Selective Communication in Nerve Nets: Impulse Specificity vs. Connection Specificity**

Presentation from the Work Session on Neurospecificity

by

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The following relates mainly to questions concerning the extent to which the specificity of nerve cells determines the kinds of connections their fibers will form. When I was first attracted to this problem back in the late 30's the evidence seemed to be going almost 100% against the idea that neuronal specificity has any influence at all in this respect. A large number of experiments had been advanced in the preceding decade and a half pointing to the conclusion that specificity among nerve cells has its effect, not on the kinds of connections that neurons form, but rather on the kinds of impulses that they conduct, and the kinds of impulses to which they selectively respond.(3,12,13,14) The further general implication was being drawn that selective communication in the vertebrate nervous system must be based, not on specific connections, but on some kind of impulse specificity or "erregungspecificität" as postulated by Dr. Weiss in his resonance principle of nervous function.

It was this latter issue in particular, impulse specificity vs. connection specificity and its critical significance

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* EDITOR'S NOTE: The three papers that follow are based on the presentations made by their authors at the Work Session. Because of what Dr. Sperry calls "long-standing theoretical differences between his own views and those of the Chairman," he does not subscribe to the Chairman's synthesis and has instead presented his original report in full, with only minor editing. Dr. Wiersma, to ensure correct understanding of his point of view, has submitted a slightly shortened version of his original presentation, with some additional remarks that amplify points raised but not fully discussed at the meeting. At the editor's request, Dr. Wall has supplied an abridgment of his original comments. -- A.H.R.

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from the standpoint of brain function, that first stimulated our own experiments in this field. The question is basic, of course, to any model for communication in neural networks. Its paramount importance above all other aspects of neural specificity was thoroughly recognized and emphatically pointed out all through the twenties, the thirties and into the early forties.

For any who may not be clear on the background material, let me repeat just briefly that the case for impulse specificity and the related resonance principle of nervous function was based mainly on the phenomenon of homologous or myotypic response already described by Dr. Weiss. Boiled down, this comes to the observation that the skeletal muscles in amphibian limbs continue to show their selective, coordinated action in spite of surgical disarrangements of the nerve connections between the muscles and the spinal centers. Because this disarrangement among the nerve connections did not interfere with either the timing or the intensity of contraction among the atypically innervated muscles, it seemed necessary to conclude that their selective activation must depend, not on specific connections, but rather up on some kind of intrinsic specificity among different modes of nerve excitation.

The view that selective patterning among neuronal connections is not critical for the normal orderly function of the nervous system was extensively supported also by many other experimental and clinical reports on the functional effects of nerve transplantations among higher vertebrates including man. The strongest support of all came from the experiments we mentioned indicating that a single regenerated motor neuron, through extra branching among supernumerary transplanted limbs, is able to activate several, up to as many as five, different nonsynergic muscles, calling up each in its separate and proper timing. It was inferred from this observation in particular that there must exist different types of nerve impulses, varying in frequency or, as suggested later, in chemical modality, with one specific mode for each of the attached muscles. It was proposed that the separate impulse types for each muscle all travel down the main stem of the axon and then become filtered out selectively at the terminal branchings, each impulse mode going to its appropriate muscle.[12,14] Impulse specficity and resonance could account for the observed selectivity of function in these experiments whereas the more traditional concepts of all-or-none transmission and connection spe ificity seemed to be effectively ruled out. We still today lack a satisfactory alternative explanation for this very crucial experimental observation.

Additional indirect support favoring the resonance interpretation came also from many experiments on nerve growth, both in vivo and in vitro, that taken together, seemed to furnish impressive demonstration of the absence of any chemical selectivity in nerve growth and the formation of nerve connections. The growth and connection of nerve fibers in neurogenesis generally was accordingly thought to be nonselective, diffuse and fortuitous, guided by factors primarily mechanical rather than chemical.(15,16)

In checking back over the experimental evidence behind this whole story it occurred to me that an alternative possible explanation had been overlooked(4,5) which, should it stand up, would not only reverse the tables in favor of connection specificity, but also would reopen the whole question of chemical selectivity in the growth and termination of nerve fibers. The reasoning here involved a complete about-face on the question of chemical selectivity; i.e., instead of following the prevailing view at the time, it went to the opposite extreme and postulated that the formation and maintenance of synaptic connections occurs with the greatest selectivity -- that, in fact, the whole process is regulated throughout by highly specific and highly refined chemical affinities between the individual neuronal elements present in any local neuropil region or other synaptic zone. This made possible a straight connectionistic interpretation for the majority of the long puzzling observations behind myotypic response and related phenomena. What the reinterpretation says in brief is that when you try to switch the nerve connections of muscles by surgical crossing and transplantation in these amphibian limbs, you are not really doing what you think you are, because as soon as you switch the peripheral connections, there is then a reaction in the centers, and the synaptic connections proceed to rearrange themselves by selective growth pressures with the result that you end up with essentially the same pattern of sensory-neuro-motor hookups that you started with. (Any selective regrowth in the periphery had long ago been ruled out.)

It was soon apparent that one dealt here not only with a new interpretation of homologous response but also with a whole new outlook for the developmental organization of behavioral nerve nets.(5,6,8,9) By combining this chemoaffinity concept of synaptic patterning with various principles of embryogenesis, like that of the morphogenetic field, induction, maturation, modulation, potentiation, differentiation, organizer effects, etc., it was possible to see a much more comprehensive

and satisfactory picture for the developmental patterning of sensory-neuro-motor circuits than anything previously available including "neurobiotaxis," the prevailing favorite among theories at the time.

When put to experimental test this chemoaffinity hypothesis began to check out with the result that many of the concepts we had formerly thought to be firmly established had to be changed.(6,8,10,17) Where we had formerly conceived of diffuse, nonselective growth pressures behind the outgrowth and termination of nerve fibers in neurogenesis, for example, it became necessary now to postulate the opposite. Where it had seemed important that we refute chemical guidance including chemotropism, chemotaxis, neurotropism, and chemical selectivity in general, our experiments now began to point to just the opposite. Where we had once thought that specific fiber connections were unimportant for orderly selective function, we had now to conclude that exactly the reverse was the case. And where it had long seemed that some kind of impulse specificity offered the only possible explanatory model for a long series of experimental observations on the functional relations between center and periphery, the more traditional connectionist scheme became again the favored and more parsimonious interpretation.

It is understandable that the about-face on these fundamental issues did not come easily for those who already had invested heavily in the opposing views. They and their followers, including myself, have allowed these extreme shifts in theoretical outlook to be effected over the years less by any frank admission of former error than by subtle shifts in terminology, the introduction of side issues and by other indirect measures. The result -- and this is the main point of all this -- has been a buildup in the literature of a complex web of ambiguity, forced terminology, and confusion of issues that is today almost impossible to untangle for anyone not intimately acquainted with the underlying history. What drew me to this Work Session in particular was the initial explanation over the phone that we "want to get things out in the open, face the issues and clarify points of controversy ... in an informal bull session with no publication duty involved." I hope we can follow through on this; it would be a genuine service to the field.

Another source of ambiguity in the literature has been the fact that most of the evidence that we were able to obtain during the 1940's and 1950's pointing to the importance of

chemical specificity in nerve growth, could also be interpreted, if one so wished, in terms of resonance and impulse specificity Take, for example, the experiment in which the midbrain of the newt Triturus viridescens was completely transected, and allowed to regenerate.(7) The demonstrated return of orderly function could be explained, as indicated initially, by assuming that the scrambled fibers of the regenerating systems unsorted themselves and grew back selectively to recover appropriate synaptic connections. There was no way to directly disprove, however, that the regrowth of connections had been non-selective, diffuse, and mechanically determined, with the orderly functional outcome being attributable to selective physiological effects like resonance and the encoding and decoding of specific impulse patterns.

It wasn't until a few years ago, in 1959 and 1960 to be exact, that we finally obtained evidence that seems to be definitive for distinguishing between the two alternative explanations. I refer to experiments with goldfish and other teleosts in which Dr. Attardi and I were able to show by direct histological methods that optic fibers arising from different sectors of the retina regenerate selectively to terminate in different prescribed sectors of the optic lobe of the midbrain.(1,2) Fibers arising from a specific quadrant of the retina refused to terminate in any but the matching quadrant of the tectum. Incorrect tectal zones were consistently bypassed and left empty.

We were able to conclude from these experiments that the regenerating optic fibers not only reconnect selectively--as long contended--but that they also preferentially select different central pathways by which to reach their proper synaptic zone. Thus we were able at long last to find definite experimental evidence for extending the chemoaffinity interpretation to include the developmental patterning of central fiber systems and brain pathways as well as the ordering of the terminal synaptic connections. This is the first situation in which we've ever been able to get a truly convincing experimental demonstration that chemical factors, rather than mechanical, are of primary importance for the orderly formation of central nervous pathways.

The differential regeneration patterns were reconstructed in these experiments from Bodian-stained serial sections in which the course of the fibers is followed on the basis of visible differences, differences, that is, between innervated and partially innervated or empty regions, between the normal fiber layers and the thicker and richer regenerated fiber

layers, between degenerating and normal fiber bundles, and in particular between the pinkish stain of newly regenerated fibers and the deep black of the older fiber systems. The results leave little further doubt that the regenerating fibers preferentially bypass denervated fiber pathways and denervated tectal regions to terminate in their proper prescribed synaptic zones,(11) under conditions where mechanical contact guidance by itself seems quite inadequate to explain the growth pattern. From the composite regeneration patterns from different retinal sectors, considered in combination with the small amount of spill-over along the edges into empty tectal regions in each case, we find evidence for a rather precise remapping of retinal points onto specific tectal foci that is particularly refined in Astronotus. That the functionally effective reconnections are quite precise has been indicated from both the behavioral and more recent electrical read-out; but these had left uncertain the extent of any diffuse, excessive, and disorderly meandering, branching and connection of fibers that would not register in the behavioral and electrical tests.

The proposed explanation for all the foregoing remains the same, namely: selective, chemotatic growth of specific fiber pathways and connections governed by an orderly pattern of specific cytochemical affinities that arise out of morphogenetic axial gradients and other forms of embryonic differentiation.

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